Double Patenting Rejections

Claims 65-72, 74, 77, and 78 were rejected under the judicially-created Doctrine of Obviousness-type Double Patenting over claims 95, 108-120, 135-175, 191-194, 196-210, 213-247, 264-274, 293-303, 317-327, 349-352, 367-370, 383-385, 389-392, 393-395, and 399-403 of U.S. Patent No. 6,270,989, and claims 73, 75, and 76 were rejected for Obviousness-type Double Patenting over claims 95, 108-120, 191-194, 196-210, 238-243, 264-271, 293-300, 317-324, 349, 367, 383, 389, and 393-395 of U.S. Patent No. 6,270,989, in view of Capecchi (Science 244:1288-1292, 1989). These rejections are being met by the filing of the enclosed terminal disclaimer, which specifies that the term of any patent issuing in the present case will not be longer than the term of the cited patent. This rejection can thus now be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 65-72, 74, 77, and 78 stand rejected under § 102(e) as being anticipated by Sherwin et al. (U.S. Patent No. 6,015,708). This rejection is respectfully traversed.

Claim 65, from which the other rejected claims depend, is drawn to a method of altering the expression of a gene in a non-immortalized primary or secondary cell. In this method, a regulatory region that alters expression of the gene is introduced into the cell by homologous recombination, so that the product of the gene is supplied by the cell.

Central to resolving this matter is an understanding of the distinction between applicants' and Sherwin's definitions of primary and secondary cells. As was stated in applicants' reply filed on June 26, 2001, primary and secondary cells, as used in the present claims, are cells that have been isolated from a vertebrate tissue source or tissue explant, prior to plating or after plating for the first time (primary cells), or such cells at subsequent stages of culturing

(secondary cells) (see, e.g., page 6, line 21 through page 7, line 4 of the specification). These types of cells are thus related to one another by the fact that the primary cells become secondary cells upon further passage.

In contrast, the primary cells of Sherwin are cells into the genomes of which an amplifiable gene and a regulatory region have been introduced by homologous recombination, and Sherwin's secondary cells, rather than being descendants of the initial, primary cells, are cells into which DNA that is removed from the primary cells is introduced. Thus, the terms "primary" and "secondary" as used by Sherwin describe cells from which DNA has been removed (the "primary" cells) and cells into which this DNA has then been introduced (the "secondary" cells).

These very different meanings of the terms primary and secondary are made clear throughout the text of Sherwin. For example, at column 2, lines 33-37, Sherwin states:

> Expression of mammalian proteins is achieved by homologous recombination, where a DNA sequence is integrated into the genome or large fragment thereof for enhancing the expression of the target gene. The modified sequence may then be transferred to a secondary host for expression. (Emphasis added.)

Further, in a section of the patent that describes the use of yeast cells, Sherwin states that "The YAC will normally be transferred from the original yeast cell to a different yeast host which is convenient for manipulation." (Column 4, lines 28-30.)

The Examiner states that applicants' arguments relating to the differences between applicants' and Sherwin's definitions of primary and secondary cells are not persuasive, because (i) applicants' definition of secondary cell would encompass essentially any cell after the first isolation of cells from an organism, and thus that any non-immortalized vertebrate cells of Sherwin would overlap with those of the present claims, and (ii) Sherwin teaches non-

immortalized primary or secondary cells at column 3, fifth full paragraph. Applicants respectfully disagree.

Included in the list at column 3, fifth full paragraph of Sherwin are cells that may well be primary or secondary (if passaged) cells, according to applicants' definitions, but they do not supply a product, as is required by the present claims. All of the cells listed in this paragraph are designated by Sherwin as being "the source of DNA" or as being employed as "the primary cells." Thus, these cells are used, according to Sherwin, as a source of DNA for transfer into other cells (Sherwin's secondary cells), in which the DNA may be expressed for protein production. These cells are not indicated as being cells into which DNA is transferred, and thus are not secondary cells (according to Sherwin's definition) and do not supply a product, as is required by the cells of the present claims.

The Examiner points to column 3, fourth full paragraph, as showing that production of a protein of interest using the methods of Sherwin can take place in a primary cell (Sherwin's definition) while, as noted in column 3, fifth full paragraph, such cells can be primary cells according to applicants' definition. Applicants respectfully disagree. The passage referred to by the Examiner must be read in context with the preceding paragraphs, which clearly show that the cells pointed to by the Examiner in the fourth full paragraph are secondary cells (Sherwin's definition), and thus the cells listed in the fifth full paragraph, which Sherwin clearly states are primary cells (Sherwin's definition) are not candidates for these cells. The relevant passages are reproduced as follows.

> The YAC library is maintained and propagated in a yeast host and homologous recombination is then employed for integrating a DNA targeting construct, usually comprising an amplifiable gene for integration into a target region comprising the target gene, which target gene encodes the protein of interest, while also

> allowing for, in the same or separate step, manipulation of the transcriptional system and/or the coding region. The modified yeast cells may then be analyzed and sequences providing for the desired modifications identified. The amplifiable region may then, as appropriate, be transformed into the expression host and the amplifiable region amplified. (Emphasis added.)
>
> "Transform" includes transform, transfect, transduce, conjugate, fuse, electroporate or any other technique for introducing DNA into a viable cell.
>
> After amplification, by employing the amplifiable gene, the transformed hosts are then screened for production of the target protein and stability and derivative cell lines are selected for desired levels of production, which cells may be expanded and used for production of the desired protein in culture. (Emphasis added.)

As can be seen in the first paragraph reproduced above (which is column 3, second full paragraph of Sherwin), the amplifiable region may be "transformed into the expression host," which means, according to Sherwin's definitions, that the amplifiable region is transferred from a primary cell into a secondary cell. Two paragraphs later, in the passage referred to by the Examiner, Sherwin notes that "the transformed hosts" are screened and can be used to produce a desired protein in culture. It is clear that "the transformed hosts" referred to here are the secondary cells with which the amplifiable region has been transformed, as noted two paragraphs above. Thus, the cells that are listed in the fifth full paragraph are not examples of cells that can be used here. Rather, as was stated in applicants' previous reply, the only cells mentioned by Sherwin for use as secondary cells, from which desired proteins are produced, as follows:

NO, "HOST" IS NOT IS DEFINED BY SHERWIN THAT WAY ..

[LOOK AT COLUMN 6, 4th FULL ¶ (2nd OF SUMMARY)]

> Various secondary mammalian expression hosts are available and may be employed. These hosts include CHO cells, particularly DHFR deficient cells, monkey kidney cells, C127 mouse fibroblasts, 3T3 mouse cells, VERO cells, etc. (Column 8, lines 52-55.)

Thus, as Sherwin does not describe primary or secondary cells (according to applicants' definitions) that supply a product, as is required by the present claims, this rejection should be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 65, 72, and 73 stand rejected under § 103(a) for obviousness over Sherwin (U.S. Patent No. 6,015,708), in view of Capecchi (Science 244:1288-1292, 1989). This rejection is respectfully traversed.

According to reasons of record, it is the Examiner's position that Sherwin differs from the claimed invention in not teaching the use of negative and positive selection markers, and that the use of such markers in the methods of Sherwin would have been obvious based on the teachings of Capecchi. In particular, the Examiner states that Capecchi teaches the use of such markers and motivation to use them would have come from Capecchi's teaching that use of these markers can lead to enrichment for desired cells.

As is noted above, Sherwin does not teach key features of applicants' invention: the use of non-immortalized primary and secondary cells to supply a product. Sherwin also does not provide any motivation to use such cells for this purpose, as Sherwin teaches that DNA is to be removed from their primary cells and then introduced into secondary cells, which are immortalized cells. The use of non-immortalized cells to supply a product, as is required by the present claims, is a concept that Sherwin does not even come close to suggesting. Capecchi does not provide what Sherwin lacks in supporting a rejection of the present claims for obviousness, as Capecchi also does not provide any suggestion to use non-immortalized primary or secondary cells, as defined by applicants, to supply a product. Thus, the teachings of Sherwin, combined

with Capecchi's teaching of positive and negative selection markers, do not support a rejection of the claimed invention for obviousness. This rejection can therefore now be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Although no charges are believed to be due, if there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: March 20, 2002

Susan M. Michaud

Susan M. Michaud, Ph.D.
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045
50010.006006 reply to office action.doc